

REMARKS**I. THE CLAIMED SUBJECT MATTER**

The above-captioned application discloses and claims a method for affecting the survival or function of neurons through the administration of a pharmaceutical composition comprising a stable, bioavailable, truncated GDNF protein products. The present invention is based on the unexpected discovery that the mature GDNF protein as disclosed by Lin et al., in U.S. Patent Application Serial No. 08/182,183 may be truncated to yield GDNF polypeptides that exhibit more stability in storage, better bioavailability and retain sufficient neurotrophic activity to promote growth of dopaminergic neurons.

II. EXPLANATION OF THE AMENDMENT**A. In the Specification**

Applicant notes the objections to the specification and respectfully requests that such objections be held in abeyance until allowable subject matter has been indicated.

B. In the Claims

Claims 30 and 45 are amended to further include a truncated GDNF polypeptide variant (Ser-Pro²³-Ile¹³⁴) specifically disclosed in the specification into the Markush group of the claims. Applicants have also amended claims 30 and 45 so that they no longer include some of the larger truncated GDNF polypeptides. These amendments have been made solely to expedite the prosecution of this application and issuance of the claims.

The amendment to claim 46 also served to include the previously mentioned truncated GDNF polypeptide variant (Ser-Pro²³-Ile¹³⁴; SEQ ID NO:51) and another specifically identified sequence (SEQ ID NO:24) into the Markush group of that claim.

The present amendment cancels claims 49 and 50 as they were withdrawn from examination by the Examiner according to 37 C.F.R. § 1.142(b). It is noted herein for the record that the subject matter of the non-elected claims 49 and 50 is not being abandoned but will instead be pursued in a

duly filed divisional application or applications to be filed in due course. Accordingly, Applicants hereby preserve the right to pursue these cancelled claims in another application(s).

1. Support for Amended Claims

Amendments to claims 30 , 45, and 46 find support throughout the specification as originally filed, and in particular on page 5, line 19.

III. CLAIM REJECTIONS AND PATENTABILITY ARGUMENTS

A. The Rejections Under Obviousness-type Double-Patenting Should Be Withdrawn

All claims under examination, i.e., claims 30 and 45-48, were also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over: (a) claims 1, 4, 10, 12, and 20 of U.S. Patent No. 5,929,041; (b) claims 1 and 5 of U.S. Patent No. 5,837,681; (c) claims 1 and 3 of U.S. Patent No. 5,731,284; (d) claims 1,3, and 8 of U.S. Patent No. 5,641,750; and (e) claims 1, 3, and 16 of U.S. Patent No.5,641,749. Applicant respectfully traverses this rejection.

As discussed in Section I hereinabove, the present invention is based on the unexpected discovery by Shaw-Fen Sylvia Hu that the mature GDNF protein as disclosed by Lin et al., in U.S. patent application serial no. 08/182,183 may be substantially truncated to yield GDNF polypeptides that exhibit more stability in storage, better bioavailability and yet retain sufficient neurotrophic activity to promote survival or function of neurons. Providing nucleic acids that encode such truncated polypeptides is not obvious to a person skilled in the art knowing Lin et al. (08/182,183) or any other prior art known at the time of the present filing because rather than pointing to the invention, Lin et al. teaches away from the present invention by disclosing a truncation of mature GDNF that would not result in the formation of an active protein (see specification, page 16, lines 16-49). It is the merit of this invention that in spite of this teaching truncation of GDNF was considered by Inventor Hu. Surprisingly, the truncated GDNF protein products have shown to exhibit an enhanced biochemical stability of the purified protein. It was determined that there was a decrease in possible degradation products, thus resulting in an considerably more storage stable protein (see specification, page 16 lines 21-25). In addition, the Applicants were the first to show that the cysteine residues of (Cys⁴¹ to Cys¹⁴³) are essential for a proper protein folding (see page 19, lines 3-6 among others). In view of Lin et al., there was no obviousness in truncating GDNF and using them in a pharmaceutical composition to affect the survival or function of neurons, nor was there any

expectation of success in the use of GDNF molecules having large truncations, let alone a reasonable expectation of their success, i.e., retaining biological activity necessary for such use. Thus, Applicants assert that the subject matter sought to be patented in the present case is not obvious in view of (a)-(e) cited above. Accordingly, the present rejection of all claims under the non-statutory doctrine of double patenting should be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, the Applicant submits that claims 30 and 45-48 are in condition for allowance and requests notification of the same.

Respectfully submitted,



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